Published in final edited form as:

J Appl Lab Med. 2020 January 01; 5(1): 158–169. doi:10.1373/jalm.2019.030023.

Consideration of Sex Differences in the Measurement and Interpretation of Alzheimer's Disease-Related Biofluid-Based Biomarkers

Michelle M. Mielke, PhD[*]

Departments of Health Sciences Research and Neurology, Mayo Clinic Rochester, MN.

Abstract

Background: The development of cerebrospinal fluid and blood-based biomarkers for Alzheimer's Disease (AD) and related disorders is rapidly progressing. Such biomarkers may be used clinically for screening the population, for enhancing diagnosis, or to help determine prognosis. Although the use of precision medicine methods have contributed to enhanced understanding of the AD pathophysiological changes and development of assays, one aspect not commonly considered is sex differences.

Content: There are several ways in which sex can affect the measurement or interpretation of biofluid biomarkers. For some markers, concentrations will vary by sex. For others, the concentrations might not vary by sex, but the impact or interpretation may vary be sex depending on the context of use (e.g., diagnostic vs prognostic). Finally, for others, there will be no sex differences in concentrations or their interpretation. This review will first provide a basis for sex differences, including differences in brain structure and function, and the means by which these differences could contribute to sex differences in biofluid concentrations. Next, the current state of sex differences in AD-related biofluid markers (i.e., amyloid-beta, phosphorylated tau, total tau, neurofilament light chain, and neurogranin) will be reviewed. Lastly, factors that can lead to the misinterpretation of observed sex differences in biomarkers (either providing evidence for or against) will be considered.

Summary: This review is intended to provide an impetus to consider sex differences in the measurement and interpretation of AD-related biofluid-based biomarkers.

[*]**Address correspondence to this author at:** Department of Health Sciences Research, Mayo Clinic, 200 first Street SW, Rochester, MN 55905. Fax: 507-284-1516; mielke.michelle@mayo.edu.

AUTHOR DISCLOSURES AND CONFLICTS OF INTERESTS

Dr. Mielke receives funding from the National Institution of Aging/National Institute of Health and unrestricted research grants from Biogen which are unrelated to the current work.

Statement of Originality: This manuscript consists of original work and it has not been previously published or presented in any context.

Keywords

Sex differences; Alzheimer's; Dementia; Biofluid-based biomarkers; Blood; Cerebrospinal fluid

Alzheimer's disease (AD) dementia is the most common form of dementia, comprising 60 to 70% of all cases. It is a progressive neurodegenerative disease that causes memory loss, cognitive deficits, and behavioral changes. With the aging of the population, the burden of AD dementia is growing to epidemic proportions. Currently more than 6 million Americans are affected and it is estimated that this number will grow to 15 million by 2050 unless new treatments or interventions to prevent or delay the onset of AD are identified (1). The hallmark pathophysiological characteristics of AD include the presence of extracellular plaques comprised of amyloid-beta (Aβ), intracellular neurofibrillary tangles comprised of abnormal phosphorylated tau protein, and neurodegeneration (2). Other molecular pathways contributing to, or potentially causing AD pathology may include inflammation, neurovascular dysfunction, senescence and accelerated aging, synaptic dysfunction, cholinergic changes, and alterations in lipid metabolism. Considering these and other pathways, there is substantial heterogeneity in the development and progression of AD dementia. Although the use of precision medicine methods have contributed to enhanced understanding of the pathophysiological changes, one aspect not commonly integrated in these approaches is sex differences.

About two thirds of persons with a clinical diagnosis of AD dementia are women because age is the greatest risk factor for AD dementia and the life expectancy for women is longer than for men (3). As a result, and similar to other aging-related diseases, the lifetime risk of AD dementia is greater for women (4, 5). Although the frequency, or count, of AD dementia is higher in women, the age-adjusted prevalence was not found to differ by sex in a meta-analysis of 45 studies (6). Sex differences in the incidence of AD dementia are less clear and may vary across countries and over time epochs (7, 8). In the United States, most studies report that the incidence of AD dementia does not differ by sex, even after the age of 85 years (9–16). Importantly, even if the incidence is similar between men and women, the underlying etiologies, symptomatology, and response to treatment can differ so the consideration of sex differences is still important (17, 18).

A complication of the many epidemiological and clinic studies assessing sex differences in the prevalence or incidence of AD is that they are generally based on a clinical diagnosis, with no information about underlying pathology. This is problematic because 10–30% of clinically defined AD dementia patients do not have AD pathology at autopsy (19, 20). Moreover, approximately 30% of the population aged 70 and older with normal cognition have elevated brain amyloid (21–23). Utilizing a biological definition provides the opportunity for a more accurate clinical diagnosis (e.g., separating AD dementia from other dementia types) and the opportunity to incorporate the preclinical phase of AD (i.e., presence of pathology before clinical symptoms are apparent), when interventions are most likely to be beneficial in slowing or halting disease progression.

Several biomarkers have been proposed for the primary pathologies of AD including Aβ plaques, neurofibrillary tangles, and neurodegeneration. Biomarkers of Aβ may include

amyloid PET, CSF Aβ42 or the CSF Aβ42/Aβ40, or blood Aβ42. Biomarkers of paired helical filament tau may include tau PET, CSF phosphorylated tau (P-tau), or blood P-tau. Lastly, biomarkers of neurodegeneration may include Fluorodeoxyglucose (FDG)-PET hypometabolism, Magnetic Resonance Imaging (MRI)-based measures of atrophy or cortical thickness in specific brain regions, CSF measures of total tau (T-tau), neurofilament light chain (NfL), and neurogranin (Ng), or blood-based measures of T-tau and NfL. However, most of these biomarkers are only used for research purposes and are not clinically available (24). Currently, three amyloid PET tracers have been approved for clinical use for the differential diagnosis of AD dementia: 18F-Florbetapir, 18F-Florbetaben, and 18F-Flutemetamol (for discussions of appropriate clinical use and benefits, see (25–27). However, in the United States amyloid PET imaging is not currently reimbursed by Medicare or insurance companies so it is rarely incorporated into clinical care. Tau PET has not been approved for clinical use.

CSF concentrations of Aβ and tau are clinically utilized in both the United States and Europe. In the United States, a lumbar puncture and measurement of CSF Aβ and tau is reimbursable but it not commonly used for AD diagnosis, especially at the population-level. Use is typically in specialty clinics to help determine etiology for atypical presentations of dementia, for dementia patients who are rapid progressors, or for young onset cases (for discussions of appropriate clinical use, see (28). CSF NfL and Ng are also promising markers of neurodegeneration but assays have not been approved for clinical use. Discussions of translating these markers to the clinic and developing reference intervals are ongoing. Lastly, there are no blood-based biomarkers that are currently approved for clinical use in the diagnosis or prognosis of AD dementia (see (29) for a comprehensive overview of potential blood-based biomarkers for AD).

With the rapidly advancing technology and development of biofluid-based biomarkers in the CSF and blood for clinical use, it is a critical time to consider factors that might affect the clinical interpretation of biomarker concentrations for the diagnosis or prognosis of AD dementia. The overarching goal of this review is to provide an impetus to consider sex differences in the measurement and interpretation of AD-related biofluid-based biomarkers. There are several ways in which sex can affect the measurement or interpretation of biofluid biomarkers. For some markers, concentrations will vary by sex. For others, the concentrations might not vary by sex, but the impact or interpretation may vary be sex depending on the context of use (e.g., diagnostic vs prognostic). Finally, for others, there will be no sex differences in concentrations or their interpretation. The review will be laid out in a sequence of topics. First, to provide a basis for sex differences, brain structural and functional differences will be described and the means by which these differences could contribute to sex differences in biofluid concentrations will be discussed. Second, the current state of sex differences in the core and up-and-coming AD-related biofluid markers (i.e., Aβ, P-tau, T-tau, NfL, and neurogranin [Ng]) will be reviewed. Lastly, factors that can lead to the misinterpretation of observed sex differences in biomarkers (either providing evidence for or against) will be considered. Throughout, sex is defined as the biological and physiological differences between women and men, with sex chromosomes (XX versus XY) and gonadal hormones primarily contributing to these differences at the cellular, organ, and systems level (30).

Sex differences in brain structure and function

There are several differences in the brain anatomy of men and women, the most notable being that men have about a 10% larger head size and cerebral brain volume compared to women (31, 32). Correspondingly, men also have greater CSF, lateral ventricles, and sulcal volumes compared to women (32–35). In addition, men have a higher percentage of white matter whereas women have a higher percentage of grey matter and higher cerebral blood flow at rest and during cognitive activity (35–37). Although many of these differences are likely due to sex hormones and sex chromosomes, the exact mechanisms are not well understood (38–40).

Sex differences in brain structure and function could contribute to differences in biofluid results. For example, there are several ways of quantifying neurodegeneration. CSF neurofilament light chain (NfL) is a marker of large-caliber subcortical axonal degeneration and studies consistently show higher levels in men compared to women (41, 42), even among cognitively unimpaired individuals without a neurodegenerative disease. A potential explanation for the higher CSF NfL concentration in men is because of the greater proportion of white matter in men's brains. Thus, sex-specific reference intervals may be needed. In addition, sex differences in brain structure and function could contribute to differences in the susceptibility to specific brain pathologies. For example, women have greater white matter hyperintensity volumes than men even after adjusting for age, hypertension, and diabetes (43). In contrast, men have a higher prevalence of cerebral microbleeds and cortical infarctions (43, 44). Blood-based biomarkers of each of these pathologies may warrant sex-specific cutpoints for screening/diagnostic or prognostic use due to differences in susceptibility and presentation of clinical symptoms.

A similar situation exists with AD pathology. An autopsy study of 141 clergy members (Catholic nuns, priests, and brothers) found that women had more global AD pathology, which was driven by more neurofibrillary tangles but not amyloid plaques (45). Subsequent autopsy studies also replicated these findings (46, 47). One of these studies demonstrated that hippocampal neurofibrillary tangles quantitatively differed by age at death and sex, with women showing more pronounced increases in neurofibrillary tangles in the hippocampus with age compared to men, suggesting a sex-specific neuroanatomic susceptibility (46, 47). In addition, for the same amount of AD pathology, these studies have reported that women were more likely to express clinical symptoms than men (45–47). Thus, a biomarker of AD pathology could have sex-specific cutpoints to enhance diagnosis either because of differences in the amount of pathology or because of differences in susceptibility. When translating these sex differences at autopsy to the development and utility of *in vivo* biomarkers of AD neuropathology, it is important to note that there can be multiple biomarkers of each pathology that provide different information. For example, Amyloid PET is a measure of aggregated amyloid plaque burden that accumulates over time. In contrast, CSF provides the concentrations of Aβ40 and Aβ42 from the lumbar sac that reflect the rates of both amyloid production and clearance. Thus, CSF Aβ is a biomarker of a pathologic state that is associated with plaque burden but is not a measure of plaque load (24).

Sex differences in AD-related biofluid-based biomarkers

Although several studies have examined CSF and blood-based biomarkers, the majority did not specifically examine whether the biomarker concentrations differ by sex, or whether the interpretion of the results differ by sex. Instead, studies adjust for sex, which treats the variable as a nuisance to be reduced or eliminated rather than trying to examine whether a sex difference exists. Thus, there is minimal literature for many markers and it is difficult to make specific recommendations about whether sex should be considered in the development of reference intervals (with the exception of a couple of markers described below). Below is a brief overview of reported sex differences, or lack of sex differences, in the current literature of core and up-and-coming AD-related biofluid-based biomarkers.

Amyloid-beta

Low, not high, concentrations of Aβ42 or the Aβ42/Aβ40 ratio are indicative of elevated brain amyloid pathology because the more brain amyloid deposited in plaques, the less available for secretion to the CSF and blood. The concentration of Aβ40 is an amyloid peptide species examined in the blood and CSF but has not been found to be altered in AD. However, some studies have suggested that the Aβ42/Aβ40 ratio is superior to the concentration of Aβ42 alone for diagnosing AD (48–51).

Cross-sectionally, sex differences have not been found in the concentrations of CSF Aβ42, Aβ40, or in the Aβ42/40 ratio (52–55). Because CSF Aβ concentrations do not appear to differ by sex, sex-specific reference intervals are not needed for diagnostic purposes (i.e., determining whether a patient has elevated brain amyloid). Longitudinally, studies have found interactions between sex and CSF Aβ42 such that for a given CSF Aβ42 concentration, women have greater declines in hippocampal atrophy and memory performance and a greater increase in CSF P-tau concentrations (54, 56). Thus, given the differential prognostic performance of CSF Aβ42 by sex, sex-specific reference intervals may need to be considered for this context of use. For example, when developing cutpoints for predicting rate of cognitive decline and neurodegeneration, a lower cutpoint may be needed for women. Such sex-specific cutpoints could be particularly useful in clinical trials to identify and enroll the men and women most likely to progress over the trial duration.

Most studies of blood Aβ42, Aβ40, or in the Aβ42/40 ratio have also not assessed sex differences in concentrations. An initial attempt to determine reference intervals of plasma Aβ1–42 using the Innotest ELISA kit among 245 individuals did not find a sex difference (57). With the continuous development of multiple assays to quantify blood Aβ, all assay platforms will need to determine if sex differences exist because some platforms measure different isoforms, for example AβN-42 vs Aβ1–42.

Phosphorylated tau

High CSF and blood P-Tau are indictive of abnormal hyperphosphorylation of the microtubule-associated protein tau. Similar to CSF Aβ, cross-sectional CSF studies of P-tau concentrations generally do not find sex differences (52–55). However, as mentioned, women with low CSF Aβ may be more susceptible to increased phosphorylated tau

concentrations (54, 56). To date, few studies have measured P-tau in the blood. The Mayo Clinic Study of Aging (MCSA) did not observe sex differences in plasma P-tau 181 concentrations (unpublished observations) (58). Other studies of plasma phosphorylated tau 181 did not examine whether concentrations differed by sex (59, 60).

Total tau

Similar to CSF P-tau, studies have not found sex differences in T-tau concentrations (41, 52–55). However, this is not surprising because the correlation between CSF P-tau and T-tau is so high across the AD clinical spectrum (spearman's rho>0.96), and sex differences in CSF P-tau concentrations have not been reported (61–63). In contrast to CSF, the correlation between plasma P-tau and T-tau is much lower (spearman's rho = 0.29) (58). A possible explanation for this discrepancy is that tau isoforms in blood differ from those in the CSF. In particular, full-length tau is the dominant isoform in plasma but not in CSF (64). Studies including Biofinder, the Alzheimer's Disease Neuroimaging Initiative (ADNI), and the MCSA, all of which used the Quanterix single-molecular array (SiMoA) platform, did not find sex differences in T-tau concentrations (65). However, a study using the immunomagnetic reduction (IMR) assay from MagQu found higher plasma T-tau concentrations in men compared to women after adjustmen for age and APOE genotype (66). The SiMoA assays measures the midregion of tau isoforms whereas the IMR assay is focused on the C terminal region of the tau protein. Whether this difference in target region of the assay is driving the disparate results in sex differences is not known, but additional research is clearly warranted. Specifically, comparative studies of mulitple platforms on the same study samples are needed to adequately compare the diagnostic and prognostic properties.

Neurofilament light chain

Neurofilament light chain (NfL) is a biomarker of subcortical large-caliber axonal degeneration across mulitple neurodegenerative disorders (67, 68). Multiple studies across the AD clinical spectrum, and in other neurodegenerative diseases, have reported higher CSF NfL concentrations among men (41, 42, 69). Whether this difference is the result of a greater vascular burden or a greater proportion of brain white matter for men compared to women is not known. However, it has been suggested that reference intervals for CSF NfL should be sex-specific (41, 42).

There are strong correlations between plasma and CSF NfL (70), and NfL in both mediums have been found to similarly associate with cognitive decline and change in cortical thickness or white matter integrity (70). Interestingly, however, plasma and serum NfL concentrations have not been found to differ by sex across the AD clinical spectrum (71, 72) or among patients with inherited peripheral neuropathies (73). The reason for the discrepancy in sex differences for NfL in the CSF versus blood, and the contributing mechanisms are not known. Regardless, given the ongoing development of reference intervals for plasma and CSF NfL, additional research is needed to identify what is contributing to the sex difference, or lack of sex differences, in order to best interpret what the values mean with regards to tracking neurodegeneration. Studies to date examining the prognostic utility of CSF or plasma NfL have not examined sex differences.

Neurogranin

Neurogranin (Ng) is a synaptic protein that is highly enriched in the dendrites, is regulated by synaptic activity, and promotes the synaptogenesis process (74). As a marker of neurodegeneration, Ng is thought to be more specific to AD compared to other neurodegenerative diseases (e.g., Parkinson's disease, Frontotemporal dementia, Huntington's disease) (75–78). In a community-based study of 777 participants, the majority (88%) of whom were cognitively unimpaired, women had higher CSF NG concentrations compared to men (41). In another study of 302 participants, Ng concentrations were higher in women than men, but did not reach significance (79). The reasons for the higher CSF concentrations of Ng among women are not known but warrant further exploration to clarify the mechanisms and to determine their clinical meaning. To date, the few studies examining blood-based measures of Ng have not found differences between AD patients and cognitively unimpaired controls, or differences in Ng concentrations by sex (80). A possible explanation for the lack of findings in blood is that the predominant endogenous CSF and human brain tissue Ng peptide consisting of amino acids 48 to 76 is not found in the blood (81).

Examples of sex-related factors that can influence the interpretation of AD-related biofluid biomarker results

There are multiple differences between women and men in anatomy and physiology across cells, tissues, organs, and systems. These differences can result from the sex chromosomes (e.g., presence of Y gene, increased doses of X genes in XX vs XY cells) or sex hormones (e.g., estrogen, testosterone). Social determinants of health that influence the physical and social environments are also important to consider. All of these differences can have marked influences on the development and progression of AD-related pathophysiology and on the measurement of related biomarkers (e.g., due to differences in protein clearance, metabolism, structure, etc.). A few examples are provided.

APOE genotype

The ε4 allele of the Apolipoprotein ε gene (*APOE*), which codes for apoE protein, is the strongest known genetic risk factor for late-onset AD (82, 83). The apoE4 protein has consistently been linked with the reduced brain clearance of Aβ and a diminished response to neuronal injury compared to the apoE3 or apoE2 proteins (84, 85). Compared to non-carriers, carriers of one ε4 allele are 3–4 times more likely to develop AD, while the risk for those with two ε4 alleles is considerably higher (83, 86).

Most studies have reported that the effects of the ε4 genotype are more pronounced in women than in men, e.g. (87–93). For example, a study of almost 58,000 participants showed that among persons aged 65–75 years with the *APOE ε3/ε4* genotype, the risk of AD dementia was four-fold higher in women compared to men (93). With regards to AD biomarkers, women APOE *ε4* carriers had higher CSF P-tau and T-tau, but not Aβ42, compared to men who were *ε4 carriers* (94). Several mechanisms underlying the interaction between sex and the *APOE* genotype on risk of AD have been proposed. For example, female *APOE* e4 knockout mice had decreased presynaptic density in the hippocampus (95)

and less of the beneficial microglial interactions with amyloid plaques compared to male mice (96). However, how the interactions between sex and *APOE* and the resulting mechanistic differences results in sex differences in concentrations of AD-associated biofluid-based biomarkers, and how such potential differences should be interpreted remain unclear.

Sex differences in blood-brain barrier permeability

The blood-brain barrier (BBB) selectively regulates the transfer of molecules between the blood, brain parenchyma, and CSF. The permeability of the BBB increases with age and in the preclinical stages of many neurodegenerative conditions, leading to the accumulation of various molecules in the brain (97). The CSF/serum albumin ratio (Q_{ALB}) is a standard way to measure BBB permeability because albumin is almost exclusively produced in the liver (98). Thus, an increased Q_{ALB} is indicative of higher permeability and potential for the transfer of proteins between the CSF and blood. A recent study of more than 20,000 patients who had undergone a lumbar puncture for any reason and 335 volunteers, aged one to 90 years, found significantly higher Q_{ALB} in men compared to women, starting around the age of 6 and up to 90 years (99). Because the sex difference was not markedly changed at puberty or menopause, it is unlikely that sex hormones explain the difference. It is possible that sex differences in CSF drainage or production could contribute to higher concentrations in men, but these mechanisms were not examined (100–102). The sex difference in Q_{ALB} is important because it could result in higher concentrations of blood-specific isoforms in the CSF and higher concentrations of CSF-specific isoforms in the blood among men. This aspect will need to be considered when examining sex differences in the concentrations of both blood and CSF AD-related biomarkers.

Sex differences in blood proteins

Plasma and serum have a higher total protein concentration and a more complex protein matrix than the CSF, which can make it difficult to accurately measure AD-related biomarkers in the blood. For example, the binding of blood Aβ42 to many proteins in plasma or serum (e.g., albumin, lipoproteins, Aβ autoantibodies, apolipoprotein J, fibrinogen, immunoglobulin, α−2-macroglobulin, apolipoprotein E, transthyretin, plasminogen, and serum amyloid p component) (103–105) can reduce the concentration of blood $Aβ_{42}$ available for measurement. Sex differences in blood protein concentrations could therefore impact the measurement of blood Aβ42 and other AD-related proteins. Indeed, sex differences in serum albumin concentrations beginning around puberty and continuing to the age of 60 have been reported (106). In addition, women have higher platelet counts and higher platelet reactivity compared to men (107, 108). Multiple studies are already examining platelet Aβ, Aβ precursor protein, and tau concentrations, but sex has typically been considered a confounder and sex-specific differences have not been examined (109–111).

Consideration of study design

Inclusion of both men and women in studies is more nuanced than just trying to enroll equal numbers. Menopausal status and subsequent hormone therapy use, comorbidities, and environment, among other factors, should be considered to optimize the generalizability and

validity of the study. If there are differences in comorbidities (e.g., kidney function) by sex, this could influence sex differences in the clearance and measurement of some AD-related biomarkers. There are also sex differences in the prevalence of vascular-related risk factors and morbidities such that men on average have more vascular risk factors and vascular events up until around the age of 70 or 75 years, at which time women catch up. The addition of vascular pathology to AD-pathology can result in earlier symptom expression. A recent autopsy study of over 1,500 community-dwelling older adults found that women were more likely than men to have mixed AD and vascular pathology (112). As discussed above, women with the same amount of AD pathology are more likely to express clinical symptoms than men (45–47). However, whether this difference is due to comorbid vascular pathology or other factors such as brain reserve remains to be examined. Thus, several sex-related differences need to be considered in study designs.

CONCLUSION

In this current era of precision medicine, it is increasingly important to consider sex differences in the etiology and progression of AD. Recent studies suggest that sex differences are observed in the concentrations of some biofluid-based biomarkers and also influence the interpretation of results. Thus, the consideration of sex differences throughout the development of AD-related biofluid-based biomarkers for clinical use is important and timely. This is especially true because most of the biofluid-based assays are still in development; comparisons across platforms and the consideration of reference intervals still need to be delineated. Thus, timing is excellent to consider whether concentrations for each marker and platform vary by sex and other factors before they are applied to clinic populations.

ACKNOWLEDGEMENTS

This work was supported by the National Institutes of Health/National Institute on Aging grants U01 AG006786, R01 AG049704, U54 AG044170, and RF1 AG055151.

Nonstandard abbreviations:

Aβ	amyloid-beta
CSF	cerebrospinal fluid
NfL	Neurofilament light chain
P-tau	phosphorylated tau
T-tau	total tau
Ng	neurogranin
ADNI	Alzheimer’s Disease Neuroimaging Initiative
MCSA	Mayo Clinic Study of Aging
SiMoA	single-molecular array

BBB	blood-brain barrier
Q_{ALB}	CSF/serum albumin ratio

Human Genes:

APOE	apolipoprotein

REFERENCES

1. Brookmeyer R, Abdalla N, Kawas CH, Corrada MM. Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. Alzheimers Dement 2018;14:121–9. [PubMed: 29233480]
2. Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12:207–16. [PubMed: 23332364]
3. Alzheimer's Association. 2017 Alzheimer's disease facts and figures. Alzheimers Dement 2017;13:325–73.
4. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 2007;29:125–32. [PubMed: 17975326]
5. Seshadri S, Wolf PA, Beiser A, Au R, McNulty K, White R, et al. Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. Neurology 1997;49:1498–504. [PubMed: 9409336]
6. Fiest KM, Roberts JI, Maxwell CJ, Hogan DB, Smith EE, Frolkis A, et al. The prevalence and incidence of dementia due to Alzheimer's disease: a systematic review and meta-analysis. Can J Neurol Sci 2016;43 Suppl 1:S51–82. [PubMed: 27307128]
7. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. Clin Epidemiol 2014;6:37–48. [PubMed: 24470773]
8. Rocca WA. Time, sex, gender, history, and dementia. Alzheimer Dis Assoc Disord 2017;31:76–9. [PubMed: 28169841]
9. Rocca WA, Cha RH, Waring SC, Kokmen E. Incidence of dementia and Alzheimer's disease: a reanalysis of data from Rochester, Minnesota, 1975–1984. Am J Epidemiol 1998;148:51–62. [PubMed: 9663404]
10. Bachman DL, Wolf PA, Linn RT, Knoefel JE, Cobb JL, Belanger AJ, et al. Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. Neurology 1993;43:515–9. [PubMed: 8450993]
11. Ganguli M, Dodge HH, Chen P, Belle S, DeKosky ST. Ten-year incidence of dementia in a rural elderly US community population: the MoVIES Project. Neurology 2000;54:1109–16. [PubMed: 10720283]
12. Kawas C, Gray S, Brookmeyer R, Fozard J, Zonderman A. Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 2000;54:2072–7. [PubMed: 10851365]
13. Hebert LE, Scherr PA, McCann JJ, Beckett LA, Evans DA. Is the risk of developing Alzheimer's disease greater for women than for men? Am J Epidemiol 2001;153:132–6. [PubMed: 11159157]
14. Kukull WA, Higdon R, Bowen JD, McCormick WC, Teri L, Schellenberg GD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. Arch Neurol 2002;59:1737–46. [PubMed: 12433261]
15. Edland SD, Rocca WA, Petersen RC, Cha RH, Kokmen E. Dementia and Alzheimer disease incidence rates do not vary by sex in Rochester, Minn. Arch Neurol 2002;59:1589–93. [PubMed: 12374497]

16. Miech RA, Breitner JC, Zandi PP, Khachaturian AS, Anthony JC, Mayer L. Incidence of AD may decline in the early 90s for men, later for women: the Cache County study. Neurology 2002;58:209–18. [PubMed: 11805246]
17. Mielke MM, Ferretti MT, Iulita MF, Hayden K, Khachaturian AS. Sex and gender in Alzheimer's disease - Does it matter? Alzheimers Dement 2018;14:1101–3. [PubMed: 30196887]
18. Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, et al. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. Alzheimers Dement 2018;14:1171–83. [PubMed: 29907423]
19. Nelson PT, Head E, Schmitt FA, Davis PR, Neltner JH, Jicha GA, et al. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. Acta Neuropathol 2011;121:571–87. [PubMed: 21516511]
20. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:322–33. [PubMed: 24450891]
21. Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Neurobiol Aging 2010;31:1275–83. [PubMed: 20472326]
22. Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, Ivnik RJ, et al. Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol 2003;62:1087–95. [PubMed: 14656067]
23. Roberts RO, Aakre JA, Kremers WK, Vassilaki M, Knopman DS, Mielke MM, et al. Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting. JAMA Neurol 2018;75:970–9. [PubMed: 29710225]
24. Jack CR Jr., Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535–62. [PubMed: 29653606]
25. Barthel H, Sabri O. Clinical Use and Utility of Amyloid Imaging. J Nucl Med 2017;58:1711–7. [PubMed: 28818990]
26. Rabinovici GD, Gatsonis C, Apgar C, Chaudhary K, Gareen I, Hanna L, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. JAMA 2019;321:1286–94. [PubMed: 30938796]
27. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Alzheimers Dement 2013;9:e106–9. [PubMed: 23809369]
28. Shaw LM, Arias J, Blennow K, Galasko D, Molinuevo JL, Salloway S, et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. Alzheimers Dement 2018;14:1505–21. [PubMed: 30316776]
29. Molinuevo JL, Ayton S, Batrla R, Bednar MM, Bittner T, Cummings J, et al. Current state of Alzheimer's fluid biomarkers. Acta Neuropathol 2018;136:821–53. [PubMed: 30488277]
30. Institute of Medicine. Exploring the Biological Contributions to Human Health: Does Sex Matter?. Washington, DC: The National Academies Press; 2001 10.17226/10028
31. Giedd JN, Raznahan A, Mills KL, Lenroot RK. Review: magnetic resonance imaging of male/female differences in human adolescent brain anatomy. Biol Sex Differ 2012;3:19. [PubMed: 22908911]
32. Gur RC, Mozley PD, Resnick SM, Gottlieb GL, Kohn M, Zimmerman R, et al. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. Proc Natl Acad Sci U S A 1991;88:2845–9. [PubMed: 2011592]
33. Grant R, Condon B, Lawrence A, Hadley DM, Patterson J, Bone I, et al. Human cranial CSF volumes measured by MRI: sex and age influences. Magn Reson Imaging 1987;5:465–8. [PubMed: 3431356]
34. Agartz I, Saaf J, Wahlund LO, Wetterberg L. Quantitative estimations of cerebrospinal fluid spaces and brain regions in healthy controls using computer-assisted tissue classification of magnetic

resonance images: relation to age and sex. Magn Reson Imaging 1992;10:217–26. [PubMed: 1564991]

35. Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P, et al. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. J Neurosci 1999;19:4065–72. [PubMed: 10234034]
36. Gur RC, Gur RE, Obrist WD, Hungerbuhler JP, Younkin D, Rosen AD, et al. Sex and handedness differences in cerebral blood flow during rest and cognitive activity. Science 1982;217:659–61. [PubMed: 7089587]
37. Lotze M, Domin M, Gerlach FH, Gaser C, Lueders E, Schmidt CO, et al. Novel findings from 2,838 adult brains on sex differences in gray matter brain volume. Sci Rep 2019;9:1671. [PubMed: 30737437]
38. Witte AV, Savli M, Holik A, Kasper S, Lanzenberger R. Regional sex differences in grey matter volume are associated with sex hormones in the young adult human brain. Neuroimage 2010;49:1205–12. [PubMed: 19796695]
39. van Amelsvoort T, Compton J, Murphy D. In vivo assessment of the effects of estrogen on human brain. Trends Endocrinol Metab 2001;12:273–6. [PubMed: 11445445]
40. Lentini E, Kasahara M, Arver S, Savic I. Sex differences in the human brain and the impact of sex chromosomes and sex hormones. Cereb Cortex 2013;23:2322–36. [PubMed: 22891037]
41. Mielke MM, Syrjanen JA, Blennow K, Zetterberg H, Skoog I, Vemuri P, et al. Comparison of variables associated with CSF neurofilament, total-tau, and neurogranin. Alzheimers Dement (in press).
42. Bridel C, van Wieringen WN, Zetterberg H, Tijms BM, Teunissen CE, and the NFLG, et al. Diagnostic value of cerebrospinal fluid neurofilament light protein in neurology: a systematic review and meta-analysis. JAMA Neurol 2019;76:1035–48.
43. Fatemi F, Kantarci K, Graff-Radford J, Preboske GM, Weigand SD, Przybelski SA, et al. Sex differences in cerebrovascular pathologies on FLAIR in cognitively unimpaired elderly. Neurology 2018;90:e466–e73. [PubMed: 29343465]
44. Graff-Radford J, Botha H, Rabinstein AA, Gunter JL, Przybelski SA, Lesnick T, et al. Cerebral microbleeds: prevalence and relationship to amyloid burden. Neurology 2019;92:e253–e62. [PubMed: 30568001]
45. Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of Alzheimer disease pathology. Arch Gen Psychiatry 2005;62:685–91. [PubMed: 15939846]
46. Liesinger AM, Graff-Radford NR, Duara R, Carter RE, Hanna Al-Shaikh FS, Koga S, et al. Sex and age interact to determine clinicopathologic differences in Alzheimer's disease. Acta Neuropathol 2018;136:873–85. [PubMed: 30219939]
47. Filon JR, Intorcia AJ, Sue LI, Vazquez Arreola E, Wilson J, Davis KJ, et al. Gender differences in Alzheimer disease: brain atrophy, histopathology burden, and cognition. J Neuropathol Exp Neurol 2016;75:748–54. [PubMed: 27297671]
48. Shoji M, Matsubara E, Kanai M, Watanabe M, Nakamura T, Tomidokoro Y, et al. Combination assay of CSF tau, A beta 1–40 and A beta 1–42(43) as a biochemical marker of Alzheimer's disease. J Neurol Sci 1998;158:134–40. [PubMed: 9702683]
49. Lewczuk P, Esselmann H, Otto M, Maler JM, Henkel AW, Henkel MK, et al. Neurochemical diagnosis of Alzheimer's dementia by CSF Abeta42, Abeta42/Abeta40 ratio and total tau. Neurobiol Aging 2004;25:273–81. [PubMed: 15123331]
50. Olsson B, Lautner R, Andreasson U, Ohrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 2016;15:673–84. [PubMed: 27068280]
51. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF Amyloid beta (Abeta) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther 2019;11:34. [PubMed: 31010420]
52. Bouter C, Vogelgsang J, Wiltfang J. Comparison between amyloid-PET and CSF amyloid-beta biomarkers in a clinical cohort with memory deficits. Clin Chim Acta 2019;492:62–8. [PubMed: 30735665]

53. Schoonenboom NS, Pijnenburg YA, Mulder C, Rosso SM, Van Elk EJ, Van Kamp GJ, et al. Amyloid beta(1–42) and phosphorylated tau in CSF as markers for early-onset Alzheimer disease. Neurology 2004;62:1580–4. [PubMed: 15136685]
54. Buckley RF, Mormino EC, Chhatwal J, Schultz AP, Rabin JS, Rentz DM, et al. Associations between baseline amyloid, sex, and APOE on subsequent tau accumulation in cerebrospinal fluid. Neurobiol Aging 2019;78:178–85. [PubMed: 30947113]
55. Li G, Shofer JB, Petrie EC, Yu CE, Wilkinson CW, Figlewicz DP, et al. Cerebrospinal fluid biomarkers for Alzheimer's and vascular disease vary by age, gender, and APOE genotype in cognitively normal adults. Alzheimers Res Ther 2017;9:48. [PubMed: 28673336]
56. Koran MEI, Wagener M, Hohman TJ, Alzheimer's Neuroimaging I. Sex differences in the association between AD biomarkers and cognitive decline. Brain Imaging Behav 2017;11:205–13. [PubMed: 26843008]
57. Zecca C, Tortelli R, Panza F, Arcuti S, Piccininni M, Capozzo R, et al. Plasma beta-amyloid1–42 reference values in cognitively normal subjects. J Neurol Sci 2018;391:120–6. [PubMed: 30103961]
58. Mielke MM, Hagen CE, Xu J, Chai X, Vemuri P, Lowe VJ, et al. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. Alzheimers Dement 2018;14:989–97. [PubMed: 29626426]
59. Shekhar S, Kumar R, Rai N, Kumar V, Singh K, Upadhyay AD, et al. Estimation of tau and phosphorylated tau181 in serum of Alzheimer's disease and mild cognitive impairment patients. PLoS One 2016;11:e0159099. [PubMed: 27459603]
60. Tatebe H, Kasai T, Ohmichi T, Kishi Y, Kakeya T, Waragai M, et al. Quantification of plasma phosphorylated tau to use as a biomarker for brain Alzheimer pathology: pilot case-control studies including patients with Alzheimer's disease and down syndrome. Mol Neurodegener 2017;12:63. [PubMed: 28866979]
61. Mattsson N, Andreasson U, Zetterberg H, Blennow K. Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. JAMA Neurol 2017;74:557–66. [PubMed: 28346578]
62. Kern S, Syrjanen JA, Blennow K, Zetterberg H, Skoog I, Waern M, et al. Association of cerebrospinal fluid neurofilament light protein with risk of mild cognitive impairment among individuals without cognitive impairment. JAMA Neurol 2019;76:187–93. [PubMed: 30419087]
63. Schindler SE, Gray JD, Gordon BA, Xiong C, Batrla-Utermann R, Quan M, et al. Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. Alzheimers Dement 2018;14:1460–9. [PubMed: 29501462]
64. Chen Z, Mengel D, Keshavan A, Rissman RA, Billinton A, Perkinton M, et al. Learnings about the complexity of extracellular tau aid development of a blood-based screen for Alzheimer's disease. Alzheimers Dement 2019;15:487–96. [PubMed: 30419228]
65. Mattsson N, Zetterberg H, Janelidze S, Insel PS, Andreasson U, Stomrud E, et al. Plasma tau in Alzheimer disease. Neurology 2016;87:1827–35. [PubMed: 27694257]
66. Chiu MJ, Fan LY, Chen TF, Chen YF, Chieh JJ, Horng HE. Plasma tau levels in cognitively normal middle-aged and older adults. Front Aging Neurosci 2017;9:51. [PubMed: 28321189]
67. Norgren N, Rosengren L, Stigbrand T. Elevated neurofilament levels in neurological diseases. Brain Res 2003;987:25–31. [PubMed: 14499942]
68. Hoffman PN, Cleveland DW, Griffin JW, Landes PW, Cowan NJ, Price DL. Neurofilament gene expression: a major determinant of axonal caliber. Proc Natl Acad Sci U S A 1987;84:3472–6. [PubMed: 3472217]
69. Mattsson N, Insel PS, Palmqvist S, Portelius E, Zetterberg H, Weiner M, et al. Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. EMBO Mol Med 2016;8:1184–96. [PubMed: 27534871]
70. Mielke MM, Syrjanen JA, Blennow K, Zetterberg H, Vemuri P, Skoog I, et al. Plasma and CSF neurofilament light: relation to longitudinal neuroimaging and cognitive measures. Neurology 2019;93:e252–e60. [PubMed: 31182505]

71. Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K. Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. JAMA Neurol 2019;76:791–9. [PubMed: 31009028]
72. Chatterjee P, Goozee K, Sohrabi HR, Shen K, Shah T, Asih PR, et al. Association of plasma neurofilament light chain with neocortical amyloid-beta load and cognitive performance in cognitively normal elderly participants. J Alzheimers Dis 2018;63:479–87. [PubMed: 29630554]
73. Sandelius A, Zetterberg H, Blennow K, Adiutori R, Malaspina A, Laura M, et al. Plasma neurofilament light chain concentration in the inherited peripheral neuropathies. Neurology 2018;90:e518–e24. [PubMed: 29321234]
74. Garrido-Garcia A, de Andres R, Jimenez-Pompa A, Soriano P, Sanz-Fuentes D, Martinez-Blanco E, et al. Neurogranin expression is regulated by synaptic activity and promotes synaptogenesis in cultured hippocampal neurons. Mol Neurobiol 2019.
75. Wellington H, Paterson RW, Portelius E, Tornqvist U, Magdalinou N, Fox NC, et al. Increased CSF neurogranin concentration is specific to Alzheimer disease. Neurology 2016;86:829–35. [PubMed: 26826204]
76. Byrne LM, Rodrigues FB, Johnson EB, De Vita E, Blennow K, Scahill R, et al. Cerebrospinal fluid neurogranin and TREM2 in Huntington's disease. Sci Rep 2018;8:4260. [PubMed: 29523800]
77. Kvartsberg H, Lashley T, Murray CE, Brinkmalm G, Cullen NC, Hoglund K, et al. The intact postsynaptic protein neurogranin is reduced in brain tissue from patients with familial and sporadic Alzheimer's disease. Acta Neuropathol 2019;137:89–102. [PubMed: 30244311]
78. Bos I, Vos S, Verhey F, Scheltens P, Teunissen C, Engelborghs S, et al. Cerebrospinal fluid biomarkers of neurodegeneration, synaptic integrity, and astroglial activation across the clinical Alzheimer's disease spectrum. Alzheimers Dement 2019;15:644–54. [PubMed: 30853464]
79. Tarawneh R, D'Angelo G, Crimmins D, Herries E, Griest T, Fagan AM, et al. Diagnostic and prognostic utility of the synaptic marker neurogranin in Alzheimer disease. JAMA Neurol 2016;73:561–71. [PubMed: 27018940]
80. De Vos A, Struyfs H, Jacobs D, Fransen E, Klewansky T, De Roeck E, et al. The cerebrospinal fluid neurogranin/BACE1 ratio is a potential correlate of cognitive decline in Alzheimer's disease. J Alzheimers Dis 2016;53:1523–38. [PubMed: 27392859]
81. Kvartsberg H, Portelius E, Andreasson U, Brinkmalm G, Hellwig K, Lelental N, et al. Characterization of the postsynaptic protein neurogranin in paired cerebrospinal fluid and plasma samples from Alzheimer's disease patients and healthy controls. Alzheimers Res Ther 2015;7:40. [PubMed: 26136856]
82. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A 1993;90:1977–81. [PubMed: 8446617]
83. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–3. [PubMed: 8346443]
84. Verghese PB, Castellano JM, Garai K, Wang Y, Jiang H, Shah A, et al. ApoE influences amyloid-beta (Abeta) clearance despite minimal apoE/Abeta association in physiological conditions. Proc Natl Acad Sci U S A 2013;110:E1807–16. [PubMed: 23620513]
85. Mahley RW, Huang Y. Apolipoprotein e sets the stage: response to injury triggers neuropathology. Neuron 2012;76:871–85. [PubMed: 23217737]
86. Bertram L, Tanzi RE. Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. Nat Rev Neurosci 2008;9:768–78. [PubMed: 18802446]
87. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997;278:1349–56. [PubMed: 9343467]
88. Payami H, Zareparsi S, Montee KR, Sexton GJ, Kaye JA, Bird TD, et al. Gender difference in apolipoprotein E-associated risk for familial Alzheimer disease: a possible clue to the higher incidence of Alzheimer disease in women. Am J Hum Genet 1996;58:803–11. [PubMed: 8644745]

89. Corder EH, Ghebremedhin E, Taylor MG, Thal DR, Ohm TG, Braak H. The biphasic relationship between regional brain senile plaque and neurofibrillary tangle distributions: modification by age, sex, and APOE polymorphism. Ann N Y Acad Sci 2004;1019:24–8. [PubMed: 15246987]

90. Liu Y, Paajanen T, Westman E, Wahlund LO, Simmons A, Tunnard C, et al. Effect of APOE epsilon4 allele on cortical thicknesses and volumes: the AddNeuroMed study. J Alzheimers Dis 2010;21:947–66. [PubMed: 20693633]

91. Damoiseaux JS, Seeley WW, Zhou J, Shirer WR, Coppola G, Karydas A, et al. Gender modulates the APOE epsilon4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels. J Neurosci 2012;32:8254–62. [PubMed: 22699906]

92. Altmann A, Tian L, Henderson VW, Greicius MD. Sex modifies the APOE-related risk of developing Alzheimer disease. Ann Neurol 2014;75:563–73. [PubMed: 24623176]

93. Neu SC, Pa J, Kukull W, Beekly D, Kuzma A, Gangadharan P, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis. JAMA Neurol 2017;74:1178–89. [PubMed: 28846757]

94. Hohman TJ, Dumitrescu L, Barnes LL, Thambisetty M, Beecham G, Kunkle B, et al. Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. JAMA Neurol 2018;75:989–98. [PubMed: 29801024]

95. Rijpma A, Jansen D, Arnoldussen IA, Fang XT, Wiesmann M, Mutsaers MP, et al. Sex differences in presynaptic density and neurogenesis in middle-aged ApoE4 and ApoE knockout mice. J Neurodegener Dis 2013;2013:531326. [PubMed: 26316992]

96. Stephen TL, Cacciottolo M, Balu D, Morgan TE, LaDu MJ, Finch CE, et al. APOE genotype and sex affect microglial interactions with plaques in Alzheimer's disease mice. Acta Neuropathol Commun 2019;7:82. [PubMed: 31113487]

97. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci 2011;12:723–38. [PubMed: 22048062]

98. Tibbling G, Link H, Ohman S. Principles of albumin and IgG analyses in neurological disorders. I. Establishment of reference values. Scand J Clin Lab Invest 1977;37:385–90. [PubMed: 337459]

99. Parrado-Fernandez C, Blennow K, Hansson M, Leoni V, Cedazo-Minguez A, Bjorkhem I. Evidence for sex difference in the CSF/plasma albumin ratio in ~20,000 patients and 335 healthy volunteers. J Cell Mol Med 2018;22:5151–4. [PubMed: 30054982]

100. Reiber H. Flow rate of cerebrospinal fluid (CSF)--a concept common to normal blood-CSF barrier function and to dysfunction in neurological diseases. J Neurol Sci 1994;122:189–203. [PubMed: 8021703]

101. Blennow K, Fredman P, Wallin A, Gottfries CG, Karlsson I, Langstrom G, et al. Protein analysis in cerebrospinal fluid. II. Reference values derived from healthy individuals 18–88 years of age. Eur Neurol 1993;33:129–33. [PubMed: 8467819]

102. Seyfert S, Kunzmann V, Schwertfeger N, Koch HC, Faulstich A. Determinants of lumbar CSF protein concentration. J Neurol 2002;249:1021–6. [PubMed: 12195448]

103. Kuo YM, Kokjohn TA, Kalback W, Luehrs D, Galasko DR, Chevallier N, et al. Amyloid-beta peptides interact with plasma proteins and erythrocytes: implications for their quantitation in plasma. Biochem Biophys Res Commun 2000;268:750–6. [PubMed: 10679277]

104. Ono K, Noguchi-Shinohara M, Samuraki M, Matsumoto Y, Yanase D, Iwasa K, et al. Blood-borne factors inhibit Alzheimer's beta-amyloid fibril formation in vitro. Exp Neurol 2006;202:125–32. [PubMed: 16806179]

105. Biere AL, Ostaszewski B, Stimson ER, Hyman BT, Maggio JE, Selkoe DJ. Amyloid beta-peptide is transported on lipoproteins and albumin in human plasma. J Biol Chem 1996;271:32916–22. [PubMed: 8955133]

106. Weaving G, Batstone GF, Jones RG. Age and sex variation in serum albumin concentration: an observational study. Ann Clin Biochem 2016;53:106–11. [PubMed: 26071488]

107. Stevens RF, Alexander MK. A sex difference in the platelet count. Br J Haematol 1977;37:295–300. [PubMed: 603762]

108. Johnson M, Ramey E, Ramwell PW. Sex and age differences in human platelet aggregation. Nature 1975;253:355–7. [PubMed: 1110780]

109. Prodan CI, Ross ED, Vincent AS, Dale GL. Differences in coated-platelet production between frontotemporal dementia and Alzheimer disease. Alzheimer Dis Assoc Disord 2009;23:234–7. [PubMed: 19812465]

110. Neumann K, Farias G, Slachevsky A, Perez P, Maccioni RB. Human platelets tau: a potential peripheral marker for Alzheimer's disease. J Alzheimers Dis 2011;25:103–9. [PubMed: 21368381]

111. Slachevsky A, Guzman-Martinez L, Delgado C, Reyes P, Farias GA, Munoz-Neira C, et al. Tau platelets correlate with regional brain atrophy in patients with Alzheimer's disease. J Alzheimers Dis 2017;55:1595–603. [PubMed: 27911301]

112. Barnes LL, Lamar M, Schneider JA. Sex differences in mixed neuropathologies in community-dwelling older adults. Brain Res 2019;1719:11–6. [PubMed: 31128096]

IMPACT STATEMENT

In the past few years, there has been rapid development of cerebrospinal fluid and blood-based biomarkers for Alzheimer's disease (AD) and related disorders. Some assays are nearing clinical use for screening or diagnostic purposes. However, one aspect not commonly considered in assay development is sex differences. There are several ways in which sex can affect the measurement or interpretation of AD-related biofluid biomarkers, including sex-differences in biomarker concentrations and sex differences in the impact or interpretation of the biomarker. This review highlights the impetus to consider sex differences in the development and interpretation of clinical assays for AD dementia and related disorders.